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IVABRADINE PROLONGS ACTION POTENTIAL DURATION AND CAUSES ATRIAL ARRHYTHMIA IN THE HEART

Poster Contributions
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Background: Ivabradine (IVA) selectively inhibits If current in the sinus node, and IKr at concentrations higher than therapeutic range. The proarrhythmic risk of IVA has not been fully determined. Sea anemone toxin-II (ATX-II, a late sodium current enhancer) -treated hearts have an increased risk of proarrhythmia and therefore was used to detect low-risk QT prolonging drugs. The objective of this study was to determine the effect of IVA on the atrial and ventricular monophasic action potential duration (MAPD) and the arrhythmic activities in the absence and presence of ATX-II.

Methods: Female rabbit isolated hearts were perfused in Langendorff mode. Hearts were paced at right atria appendage. Left atrial and ventricular MAPD90 were analyzed.

Results: When hearts were paced at 2.8 Hz, the atrial, and endocardial and epicardial ventricular MAPD90 were 49.6 ±3, 136.3±7 and 127.4±4 ms, respectively. IVA (3-10μM) significantly prolonged these MAPD90 by 15.9±2 (n=6, $p<0.01$), 31.5±4 and 23.9±3 ms, respectively (n=6, $p<0.01$), in concentration dependent manners. When the pacing rate was increased from 2.5 Hz to 3.5 Hz, IVA (6 μM) reduced LV endocardial and epicardial MAPD90 by 41.2±3 and 31.6±4 ms (n=5, $p<0.05$) in a reverse rate dependent mode. ATX-II (3 nM) prolonged atrial MAPD90 by 36.5±5 ms, and LV endocardial and epicardial MAPD90 by 19.9±3 and 19.5±4ms. In the continued presence of ATX-II (3 nM), IVA (6-10 μM) reduced the atrial MAPD90 by 14.4±4 ms (n=6, $p<0.01$). Atrial arrhythmias were observed in 4 of 12 (33.3%) hearts treated with 1-10μM IVA in the presence of 3 nM ATX-II. In contrast, IVA (3-10 μM) caused greater prolongations in presence than in absence of ATX-II, on LV endo- and epi- cardial MAPD90 by 36.2±7 and 27.5±5 ms (n=6, $p<0.01$). IVA did not increase the BVR of MAPD90 and transmural dispersion of MAPD90, and caused no ventricular arrhythmias both in the absence and presence of ATX-II (n=6, $p>0.05$).

Conclusion: IVA prolongs both atrial and ventricular MAPD and causes atrial arrhythmias in hearts when late sodium current is increased, without proarrhythmic activities in the ventricles. This result may explain the characteristics of IVA in clinical studies.